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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/088,724 | 06/14/2002 | Ikuo Nishimoto | 082377-00000US | 6929 |

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| EXAMINER | |
|---|---|
| CHERNYSHEV, OLGA N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

DATE MAILED: 04/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/088,724 | NISHIMOTO, IKUO | |
| | Examiner | Art Unit | |
| | Olga N. Chernyshev | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-8,13,15,16 and 20-45* is/are pending in the application.

4a) Of the above claim(s) *35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-8, 13, 15-16, 20- 34 and 36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/20/4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

1. Claims 1, 2, 5, 6, 8, 13 have been amended, claims 14 and 18 have been cancelled and claims 20-45 have been added as requested in the amendment filed on September 20, 2004. Following the amendment, claims 1, 2, 4-8, 13, 15-16, 20-45 are pending in the instant application.

2. Newly submitted claim 35 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claim does not recite SEQ ID NO: 5, which is the sequence of elected polypeptide (see election of Paper filed on October 16, 2003).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 35 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 1, 2, 4-8, 13, 15-16, 20- 34 and 36-45, in so far as they encompass a polypeptide of SEQ ID NO: 5 are under examination in the instant office action.

4. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

6. Applicant's arguments filed on September 20, 2004 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 4-8, 13, 15 and 16, as amended, are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 1, 4-8, 13, 15 and 16 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the reply filed on September 20, 2004. In that paper, applicant has stated that "[t]he sequence listing in amended claim 1 (identified by the sequence identifier SEQ ID NO: 64) is in fact in the sequence listing" (bottom at page 18 of the Response). The sequence recited in claim 1, however, as currently amended, is identified as SEQ ID NO: 63. These statements indicate that the invention is different from what is defined in the claim(s) because the sequence recited in claim 1, as originally filed, appears to be identical as the sequence presented on page 9 of the instant specification, as originally filed, which was identified as SEQ ID NO: 61 in the amendment to the specification filed on January 29, 2004. Moreover, the sequence of SEQ ID NO: 63, as submitted within the sequence listing filed on Sept 20, 2004, appears to be limited to 10 amino acids, however, according to the specification amended on January 29, 2004, SEQ ID NO: 63 is limited to four amino acids. Both "versions" of polypeptide of SEQ ID NO: 63 do not appear to have any resembles to the sequence of the polypeptide recited in claim 1, as amended.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 20-22, 28-34, 36-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-22, 28-30 and 36-38 encompass polypeptides of Formula IV represented by SEQ ID NOs: 100-102, which are allegedly originally recited on pages 9-10 of the instant specification, as originally filed (see page 17 of the Response). However, there appears to be no reference to Formula IV or the above recited sequences within the text on pages 9-10. Therefore, the newly submitted claims 20-22, 28-34, 36-38 are directed to the new matter not originally presented in the specification, as filed.

Claims 31-34 encompass negative limitations (DNA which "does not comprise the nucleotide sequence of SEQ ID NO: 4"), which are not supported by the instant specification, as originally filed.

11. Claims 2, 4-8, 13, 15-16, 23-27, 31-34, 39-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record as applied to claims 2, 4-8, 13-16 and 18 in section 8 of Paper mailed on March 16, 2004.

Applicant traverses the rejection on he premises that he instant specification provides enough guidance and working examples on how to make the recited and currently claimed proteins (pages 20-21 of the Response). Applicant's arguments have been fully considered but are not deemed to be persuasive for the reasons that follow.

First, Applicant is reminded that the examination of the instant specification is limited to the elected subject matter, which is a polypeptide of SEQ ID NO: 5 (see election of Paper filed on October 16, 2003). While it is true that the instant specification provides disclosure of plurality of different polypeptides asserted to have the ability to suppress neuronal death associated with Alzheimer's disease, yet the claimed subject matter includes polypeptides that have no structural similarity or relation to the instant polypeptide of SEQ ID NO: 5 or any polypeptides recited in the instant specification. Note that although the claimed polypeptides are not limited to the specific recited sequences, with regard to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed subject matter is one of a polypeptide, which has homology to a polypeptide with "one to five amino acids [being] substituted, deleted, inserted, and/or added". One skilled in the art readily appreciates that the result of such substitution, deletion and/or addition of one to five amino acid to the given polypeptide of SEQ ID NO: 5 will lead to a completely altered structure with no similarity to the original twenty-four amino acid long polypeptide of SEQ ID NO: 5. The instant specification does not provide any guidance on how to make polypeptides, which meet all the structural limitations recited in the claims, such polypeptides that suppress neuronal death associated with Alzheimer' disease.

12. Claims 2, 4-8, 13, 15-16, 23-27, 31-34, 39-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as applied to claims 2, 4-8, 13-16 and 18 in section 9 of Paper mailed on March 16, 2004.

Applicant argues that the instant specification provides sufficient number of examples of polypeptides with various deletion and addition to the structure of polypeptide of SEQ ID NO: 5, which retained the function of being able to suppress neuronal death and relates to *Vas-Cath Inc. v. Mahurkar* case law and PTO Written Description Guidelines (pages 26-28 of the Response). Applicant's arguments have been carefully considered but are not deemed to be persuasive for the following reasons.

Claims 2, 4-8, 13, 15-16, 23-27, 31-34, 39-45 encompass a genus of polypeptides with limited or no structural similarity to the polypeptide of SEQ ID NO: 5 of the instant invention. Because the instant specification fails to describe the claimed molecular embodiments (those polypeptides, which have homology to a polypeptide of SEQ ID NO: 5, wherein one to five amino acids within the polypeptide sequence have been substituted, deleted, and/or added), one cannot envision the structure of the claimed molecules. The specification describes a protein having the amino acid sequence of SEQ ID NO: 5 and proteins, which are similar to the protein of SEQ ID NO: 5, however, the claimed genus encompasses a vast number of species that have no structural similarity to the protein of SEQ ID NO: 5 or to any currently disclosed polypeptides. The instant specification fails to describe any other protein which lacks the amino acid sequence of SEQ ID NO: 5 and has the activities possessed by the isolated protein.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, for reasons of record fully explained earlier and reasons above, claims 2, 4-8, 13, 15-16, 23-27, 31-34, 39-45 do not meet the written description provision of 35 U.S.C. §112, first paragraph.

13. Claims 13, 15-16 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record as applied to claims 13-16 in section 10 of Paper mailed on March 16, 21004.

Beginning at page 22 of the Response, Applicant argues that "[t]he Specification establishes a correlation between in vitro and in vivo activity of the claimed polypeptides" and

refers to case law *Cross v. Izuka*. Applicant submits that because the specification teaches that the claimed polypeptides produced neuroprotective effect for primary neuronal cultures exposed to Aβ *in vitro* and because there is a link between Aβ and Alzheimer's disease, "the claimed polypeptides would be reasonably expected to do so in vivo in a human" (top at page 23). Applicant further refers to two publications, which provide additional data that the claimed polypeptide(s) had similar neuroprotective action *in vitro* in different groups of neurons and also improved learning and memory when intracerebrally administered to mice (middle at page 23). Applicant's arguments have been fully considered but are not persuasive for the following reasons.

Claims 13-16 and 45 are directed to pharmaceutical compositions comprising polypeptide of SEQ ID NO: 5 or a vector into which a DNA encoding the polypeptide of SEQ ID NO: 5 is inserted. With regards to pharmaceutical compositions comprising DNA, one readily understands that neither knowledge in the art nor the instant specification, as filed, provide an adequate enablement for using the claimed compositions for purposes of successful gene therapy. Further, as correctly pointed out by Applicant, in *Cross vs. Izuka* the court held that reasonable correlation between *in vitro* and *in vivo* exists where the disclosure of the pharmaceutical activity is reasonably based on the probative evidence. However, in the instant case the specification fails to provide any evidence or sound scientific reasoning to support a conclusion that neuroprotective effect of the claimed polypeptide as shown *in vitro* for neuronal cultures treated with Aβ could be directly extrapolated to a successful prevention or treatment of neurodegeneration, for example (see claim 15).

In the decision *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970), the court held that

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved", emphasis added.

In order to practice the claimed pharmaceutical composition comprising a polypeptide of SEQ ID NO: 5, a skilled practitioner would have to resort to a substantial amount of undue experimentation to discover if a neuroprotective action of that polypeptide, as shown in experimental primary neuronal cultures, would be effective when systemically administered to a subject to prevent or treat Alzheimer's disease or any other neurodegenerative condition. One skilled in the art readily appreciates that Aβ toxicity is one of many other possible pathological factors in etiology of Alzheimer's; therefore, one would not expect to prevent or treat

Alzheimer's disease by possibly interfering with Aβ neurotoxicity. Moreover, there appears to be no evidence or reasoning presented in the instant specification, as filed, that administration of a polypeptide of SEQ ID NO: 5 would prevent or treat any neurodegenerative condition, including pathologies not associated with Aβ toxicity.

Applicant argues that "the Specification provides extensive teaching on the route, duration and quantity of administration of the claimed polypeptides for use in a pharmaceutical composition" (bottom at page 23). However, the general information on administration of pharmaceutical compositions, which is provided at pages 20-21 of the instant specification, clearly cannot satisfy a skilled practitioner. The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. In the instant case, while any person skilled in the art appreciates that "[e]xample of suitable administration methods include percutaneous, intranasal, transbronchial, intramuscular, intraperitoneal, intravenous, intraspinal, intracerebroventricular, or oral administration" (middle at page 20), there appears to be not further support provided in the instant specification, as filed, to guide one skilled in the art on how to use the pharmaceutical composition comprising a polypeptide of SEQ ID NO: 5 for oral administration, for example.

Therefore, for reasons fully explained earlier and reasons above, the instant rejection is maintained.

***Conclusion***

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December

28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1646

April 11, 2005